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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/444,335	11/19/1999	GRIGORI N. ENIKOLOPOV	JUV-2 RCE2	8515

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FISH & NEAVE IP GROUP
ROPES & GRAY LLP
1251 AVENUE OF THE AMERICAS FL C3
NEW YORK, NY 10020-1105

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/444,335	ENIKOLOPOV ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-13,16-21,24-50,72-74 and 77* is/are pending in the application.

4a) Of the above claim(s) *25-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-13,16-21,24,72-74 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 4/12/05. Claims 6, 7, 14, 15, 22, 23, 51-71, 75, 76, 78, and 79 were canceled as requested. Claims 1-5, 8-13, 16-21, 24-50, 72-74, and 77 remain pending. Claims 25-50 were withdrawn from consideration in Paper No. 13, as being drawn to a non-elected invention. Applicant timely traversed the restriction requirement in the response filed 9/11/2000.

Claims 1-5, 8-13, 16-21, 24, 72-74, and 77 are under consideration in this Office Action.

Drawings

The drawings stand objected to for the reasons indicated in the PTO form 948 accompanying Paper No. 13, issued 10/4/00.

Rejections Withdrawn

The rejection of claim 24 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendments providing proper antecedent basis for "the promoter and second intron, or fragment thereof".

The rejection of claims 16 and 24 under 35 U.S.C. 112, first paragraph for new matter is withdrawn in view of Applicant's amendments eliminating the new matter. Note that Applicant's amendments necessitated a new rejection of these claims for new matter.

The rejection of claims 1-5, 8-13, 17, and 19-21 under 35 USC 102 over Zimmerman et al is withdrawn in view of the amendment requiring expression of enhanced green fluorescent protein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1-3, 5, 8-11, 13, 16, 17, 19-21, 24, 72-74, and 77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5, 8-11, 13, 16, 17, 19-21, 24, 72-74, and 77 have been amended to be drawn to the genus of transgenic rodents, progeny or embryos thereof, comprising a nucleic acid sequence encoding enhanced green fluorescent protein operably linked to a regulatory sequence comprising a mammalian nestin promoter and mammalian nestin second intron or second intron fragment, wherein the gene coding for the enhanced green fluorescent protein is expressed in multipotent stem and progenitor cells of the rodents, progeny, or embryos. The term "rodent" is not disclosed in the specification as

filed. The only species of the genus "rodent" disclosed in the specification as filed are rats and mice. The genus of rodents embraces diverse organisms including squirrels, beavers, woodchucks, guinea pigs, hamsters, porcupines, and other small gnawing mammals with constantly growing incisors. The disclosure of the two closely related species, rats and mice, does not suffice as a representative number of species of this diverse genus, and one of skill in the art could not conclude that Applicant had possession of, or had contemplated claiming, the genus of rodents at the time the invention was filed.

Scope of Enablement

Claims 1-5, 8-13, 16, 17, 19-21, 24, 72-74, and 77 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic rat or mouse, or progeny or embryo thereof, comprising a nucleic acid sequence encoding enhanced green fluorescent protein operably linked to a regulatory sequence comprising a mammalian nestin promoter and mammalian nestin second intron or second intron fragment, wherein the gene coding for the enhanced green fluorescent protein is **selectively** expressed in multipotent stem and progenitor cells of the rat or mouse, progeny, or embryo, does not reasonably provide enablement for non-rat or non-mouse transgenic mammals, progeny, or embryos in which enhanced green fluorescent protein is expressed in cells other than multipotent stem and progenitor cells of the non-rat or non-mouse mammal, progeny or embryo. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention encompasses a nonhuman transgenic rodent or mouse, progeny, or embryo thereof, comprising a nucleic acid sequence encoding green fluorescent protein operably linked to a regulatory sequence comprising a mammalian nestin promoter and second intron wherein the gene coding for the green fluorescent protein is expressed in multipotent stem and progenitor cells of the mammal, progeny, or embryo. Independent claims 1, 9, and 72 require expression in multipotent stem and progenitor cells of the rodent or mouse, but only certain dependent claims (2, 10, 20, and 73) require *selective* expression in those cells. As such, claims 1, 3-5, 8, 9, 11-13, 16, 17, 19, 21, 24, 72, and 77 are not limited in terms of the other types of cells in which the marker is expressed, and may be interpreted as embracing rodents in which all cells express the marker protein. This type of result could occur if, for example, the transgene construct integrated downstream of the promoter of a house keeping gene and expression of the transgene was subsequently influenced by the house keeping gene promoter.

The specification teaches that the claimed rodent may be used to facilitate isolation or detection of multipotent stem and precursor cells. It follows that in order to function as intended, the marker protein should be expressed selectively in multipotent stem and progenitor cells of the rodent, rather than in a large proportion of cells or in all cells. If the marker is expressed non-selectively, then one cannot take advantage of the fluorescence to identify or isolate multi-potent stem and precursor cells. The

specification does not teach how to use the scope of claimed rodents in which expression of the marker does not occur selectively in multipotent stem and progenitor cells, and one of skill in the art would have to perform undue experimentation in order to use these rodents as intended in the specification.

Claims 1-3, 5, 8-11, 13, 16, 17, 19-21, 24, 72-74, and 77 embrace non human transgenic rodents that express a green fluorescent protein in multipotent stem and progenitor cells, whereas the specification exemplifies a transgenic mouse which selective express a green fluorescent protein in such cells. In view of the fact that the working example in the specification uses a rat nestin promoter/enhancer operably linked to GFP to express GFP in a mouse, the scope of transgenic rats is also considered to be enabled. However, as discussed above under written description, the scope of "rodents" represents new matter, so this scope cannot be considered to be enabled by the specification as filed, particularly in view of the unpredictability in the art of obtaining similar phenotypes in diverse transgenic organisms as discussed in the previous action of 10/12/04.

Response to Arguments.

Applicant's arguments filed 4/12/05 have been completely considered, but are unpersuasive. Applicant asserts that the claims are enabled in view of the amendments limiting the scope of the transgenic animal to a transgenic rodent. This assertion is unpersuasive because it is only a statement of opinion unsupported by evidence or argument. Note that the scope of the invention considered to be enabled

has been broadened to embrace rat and mouse. However, as discussed above, the scope of "rodent" cannot be considered to be enabled by the specification as filed because this scope was not contemplated in the specification as filed and represents new matter. Applicant did not directly address the issue of how to use the embraced species of rodent in which expression of GFP is not limited to multipotent stem and progenitor cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8-13, 16-21, and 24, are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman (1994) in view of Chiochetti (1997) and Zhang et al (Biochem. Biophys. Res. Comm. 227: 707-711 (1996).

Zimmerman taught transgenic mice comprising a construct containing a lac Z reporter transgene under the control of the promoter and second intron enhancer of the rat nestin gene. Beta galactosidase was expressed in neuronal stem cells of the resulting animals, and allowed measurement of these cells. The mice were made by microinjection of recombinant expression constructs in to the pronuclei of fertilized mouse eggs. See entire document, especially Abstract; Table I, pages 12, 13,

particularly constructs B, C, and F; Fig. 2 on page 15; and page 23, fourth full paragraph.

Zimmerman did not teach a construct comprising enhanced green fluorescent protein.

Chiochetti taught that green fluorescent protein (GFP) is a more powerful and sensitive tool for studying gene expression in transgenic animals than is beta galactosidase. GFP fluorescence easily identified a greater number of positive cells than beta galactosidase, and the pattern generated by GFP more closely matched the endogenous gene expression as measured by in situ hybridization. See entire document, especially abstract; sentence bridging pages 193 and 194; page 199, column 1, first two full paragraphs; page 202, column 1, lines 5-7.

Zhang taught an enhanced version of GFP that was 35-times brighter than wild type GFP and was codon optimized for expression in mammalian cells, thus greatly increasing the sensitivity of the reporter. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Zimmerman by substituting a green fluorescent protein for beta galactosidase, and to study gene expression in neuronal stem cells in living animals and their organs and tissues. One would have been motivated to do so because Chiochetti teaches that green fluorescent protein (GFP) is a more powerful and sensitive tool for studying gene expression in transgenic animals than is beta galactosidase. One would have been motivated to select enhanced GFP in order to take advantage of the increased fluorescence and mammalian codon usage.

Thus the invention as a whole was *prima facie* obvious.

Claims 1-5, 8-13, 16-21, 24, 72-74, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman (1994) in view of Yamaguchi et al (Neuroscience Research Supplement 22: S286, (1998)) and Zhang et al (Biochem. Biophys. Res. Comm. 227: 707-711 (1996).

Zimmerman taught transgenic mice comprising a construct containing a lac Z reporter transgene under the control of the promoter and second intron enhancer of the rat nestin gene. Beta galactosidase was expressed in neuronal stem cells of the resulting animals, and allowed measurement of these cells. The mice were made by microinjection of recombinant expression constructs in to the pronuclei of fertilized mouse eggs. See entire document, especially Abstract; Table I, pages 12, 13, particularly constructs B, C, and F; Fig. 2 on page 15; and page 23, fourth full paragraph.

Zimmerman did not teach a construct comprising green fluorescent protein.

Yamaguchi taught adult transgenic mice comprising a GFP gene under the control of a nestin promoter. Neuronal stem cells could be easily visualized in vivo in the mice. Yamaguchi was silent as to the nature of the regulatory control regions present in the promoter. See abstract.

Zhang taught an enhanced version of GFP that was 35-times brighter than wild type GFP and was codon optimized for expression in mammalian cells, thus greatly increasing the sensitivity of the reporter.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Zimmerman by substituting a green fluorescent protein for beta galactosidase, and to study gene expression in neuronal stem cells in living animals and their organs and tissues. One would have been motivated to do so because Yamaguchi teaches that GFP allows visualization of neuronal stem cells in vivo, and that study of such cells in vivo would lead to an understanding of the process of organization and plastic changes of the neuronal circuit during development and in adults. See abstract. One would have been motivated to select enhanced GFP in order to take advantage of the increased fluorescence and mammalian codon usage.

Response to Arguments

Applicant's arguments, filed 4/12/05 have been fully considered as they may apply to the rejections above, but they are not persuasive.

Applicant asserts at pages 24 and 26 of the response that Zimmerman does not teach or suggest the use of any type of fluorescent protein for measurement of gene expression in a rodent, and that Chiochetti fails to teach the use of an enhanced green fluorescent protein. This is unpersuasive because, in response to Applicant's amendment requiring enhanced green fluorescent protein, new grounds of rejection have been made including the Zhang (1996) reference which discloses the superiority of enhanced GFP. For these reasons the rejections are considered proper.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax

number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.